

JC03 Rec'd PCT/PTO 11 SEP 2001

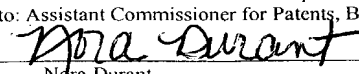
FORM PTO-1390 OFFICE (REV 11-2000)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK		ATTORNEY'S DOCKET NUMBER  280502000200	
<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. § 371</b>				U.S. APPLICATION NO. (If known, see 37 CFR 1.5)  <b>09/936887</b>	
INTERNATIONAL APPLICATION NO <b>PCT/CA00/00266</b>		INTERNATIONAL FILING DATE  <b>March 13, 2000</b>		PRIORITY DATE CLAIMED  <b>March 12, 1999</b>	
TITLE OF INVENTION <b>METHODS AND COMPOSITIONS FOR TREATING LEUKEMIA</b>					
APPLICANT(S) FOR DO/EO/US  <b>Chaim M. ROIFMAN, et al.</b>					
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information					
1	<input checked="" type="checkbox"/>	This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.			
2	<input type="checkbox"/>	This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371			
3	<input type="checkbox"/>	This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below			
4	<input type="checkbox"/>	The US has been elected by the expiration of 19 months from the priority date (PCT Article 31)			
5	<input checked="" type="checkbox"/>	A copy of the International Application as filed (35 U.S.C. 371(c)(2))			
	a.	<input checked="" type="checkbox"/>	is attached hereto (required only if not communicated by the International Bureau).		
	b.	<input type="checkbox"/>	has been communicated by the International Bureau.		
	c.	<input type="checkbox"/>	is not required, as the application was filed in the United States Receiving Office (RO/US).		
6	<input type="checkbox"/>	An English language translation of the International Application under PCT Article 19 (35 U.S.C. 371(c)(2)).			
	a	<input type="checkbox"/>	is attached hereto.		
	b.	<input type="checkbox"/>	has been previously submitted under 35 U.S.C. 154(d)(4).		
7	<input checked="" type="checkbox"/>	Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).			
	a.	<input type="checkbox"/>	are attached hereto (required only if not communicated by the International Bureau)		
	b.	<input type="checkbox"/>	have been communicated by the International Bureau.		
	c.	<input type="checkbox"/>	have not been made; however, the time limit for making such amendments has NOT expired.		
	d.	<input checked="" type="checkbox"/>	have not been made and will not be made.		
8	<input type="checkbox"/>	An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3))			
9	<input type="checkbox"/>	An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).			
10	<input type="checkbox"/>	An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).			
<b>Items 11. to 16. below concern document(s) or information included:</b>					
11	<input type="checkbox"/>	An Information Disclosure Statement under 37 CFR 1.97 and 1.98.			
12	<input type="checkbox"/>	An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.			
13	<input checked="" type="checkbox"/>	A <b>FIRST</b> preliminary amendment.			
14	<input type="checkbox"/>	A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment			
15	<input type="checkbox"/>	A substitute specification.			
16	<input type="checkbox"/>	A change of power of attorney and/or address letter.			
17	<input type="checkbox"/>	A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.			
18	<input type="checkbox"/>	A second copy of the published international application under 35 U.S.C. 154(d)(4)			
19	<input type="checkbox"/>	A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4)			
20	<input checked="" type="checkbox"/>	Other items or information: return receipt postcard.			

**CERTIFICATE OF MAILING BY "EXPRESS MAIL"**

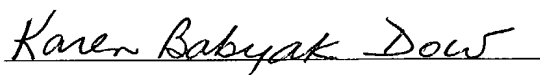
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Date of Deposit: September 11, 2001

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 Nora Durant

JC16 Rec'd PCT/PTO SEP 11 2001

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) <b>09/936887</b>		INTERNATIONAL APPLICATION NO. <b>PCT/CA00/00266</b>		ATTORNEY'S DOCKET NUMBER: <b>280502000200</b>	
21. <input checked="" type="checkbox"/> The following fees are submitted: <b>BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):</b> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO.....\$1,000.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO.....\$860.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....\$710.00 International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provision of PCT Article 33(1)-(4) .....\$690.00 International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) .....\$100.00				<b>CALCULATIONS</b> <b>PTO USE ONLY</b>	
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$860.00	
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$130.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	37 - 20 =	17	x \$18.00	\$306.00	
Independent claims	3 - 3 =	0	x \$80.00	\$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$270.00	\$	
TOTAL OF ABOVE CALCULATIONS =				\$436.00	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.				\$	
SUBTOTAL =					
Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+	\$
TOTAL NATIONAL FEE =				\$860.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00 per property</b>				+	\$
TOTAL FEES ENCLOSED =				\$1296.00	
				Amount to be refunded:	\$*
				charged:	\$1296.00
a. <input type="checkbox"/> A check in the amount of \$___ to cover the above fees is enclosed. b. <input checked="" type="checkbox"/> Please charge my <b>Deposit Account No. 03-1952</b> in the amount of \$1,296.00 to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to <b>Deposit Account No. 03-1952</b> . A duplicate copy of this sheet is enclosed. d. <input type="checkbox"/> Fees are to be charged to a credit card. <b>WARNING:</b> Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.					
<b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b>					
SEND ALL CORRESPONDENCE TO:					
Karen B. Dow Morrison & Foerster LLP 3811 Valley Centre Drive Suite 500 San Diego, California 92130-2332			 SIGNATURE Karen B. Dow Registration No. (29,684)		

09/09/2001 JC16 Rec'd PCT/PTO SEP 11 2001  
09/936887 PATENT

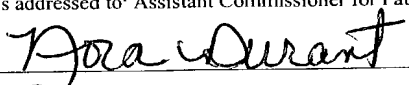
Docket No. 280502000200  
International Application No. PCT/CA00/00266

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Nora Durant

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In the application of:

Chaim M. ROIFMAN, et al.

Serial No.: Not Yet Assigned

Filing Date: Herewith

International Application No. **PCT/CA00/00266**

International Filing Date **March 13, 2000**

For: **METHODS AND COMPOSITIONS FOR  
TREATING LEUKEMIA**

Examiner: Not Yet Assigned

Group Art Unit: Not Yet Assigned

**PRELIMINARY AMENDMENT**

Assistant Commissioner for Patents  
BOX PCT  
Washington, D.C. 20231

Dear Sir:

This is a preliminary amendment prior to examination, please amend the application as follows:

In the Specification:

On page 1 of the specification, under the title, please amend by inserting the following:

Please create a new page of the specification for the abstract as follows:

-- Compounds of general formula (I), wherein R<sub>1</sub> is H or C1 to C3 alkyl; R<sub>2</sub> is aryl or -(CH<sub>2</sub>)<sub>n</sub>-aryl and n is 1 to 4; R<sub>3</sub> is H or CH<sub>3</sub>; and R<sub>4</sub> is substituted or unsubstituted phenyl, pyridyl, thiophene, furan, indole, pyrrole, thiazole or imidazole are described, as well as methods for treating cell proliferative disorders and neoplastic disorders.--

In the Claims:

Please replace Claims 34-36 as follows:

(Amended) 34. A method in accordance with claim 23 wherein the neoplastic disorder is a lymphoma, a leukemia or a metastatic carcinoma.

(Amended) 35. A method in accordance with claim 34 wherein the neoplastic disorder is Acute Lymphoblastic Leukemia.

(Amended) 36. A method for treating a cell proliferative disorder in a mammal comprising administering to the mammal an effective amount of a compound in accordance with claim 1.

Enclosed is the following Exhibit A:

Exhibit A: Marked-up Version of Amendments to the Claims.

### Remarks

The claims have been amended to eliminate multiple claim dependencies. The changes to the claims are editorial and do not constitute new matter. Entry of the amendment is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition

PATENT  
Docket No. 280502000200  
International Application No. PCT/CA00/00266

for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 280502000200.

However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: September 11, 2001

By: Karen Babyak Dow  
Karen B. Dow  
Registration No. 29,684

Morrison & Foerster LLP  
3811 Valley Centre Drive  
Suite 500  
San Diego, California 92130-2332  
Telephone: (858) 720-7960  
Facsimile: (858) 720-5125

EXHIBIT A

MARKED-UP VERSION OF AMENDMENTS TO THE CLAIMS

(Amended) 34. A method in accordance with [any one of claims 23 to 33] claim 23 wherein the neoplastic disorder is a lymphoma, a leukemia or a metastatic carcinoma.

(Amended) 35. A method in accordance with [any one of claims 23 to 33] claim 34 wherein the neoplastic disorder is Acute Lymphoblastic Leukemia.

(Amended) 36. A method for treating a cell proliferative disorder in a mammal comprising administering to the mammal an effective amount of a compound in accordance with [any one of claims 1 to 11] claim 1.

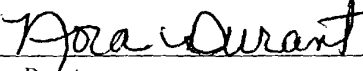
JC16 Rec'd PCT/PTO SEP 11 2001  
PATENT  
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09/936887

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Nora Durant

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In the application of:

Chaim M. ROIFMAN, et al.

Serial No.: Not Yet Assigned

Filing Date: Herewith

International Application No. **PCT/CA00/00266**

International Filing Date **March 13, 2000**

For: **METHODS AND COMPOSITIONS FOR  
TREATING LEUKEMIA**

Examiner: Not Yet Assigned

Group Art Unit: Not Yet Assigned

**PRELIMINARY AMENDMENT**

Assistant Commissioner for Patents  
BOX PCT  
Washington, D.C. 20231

Dear Sir:

This is a preliminary amendment prior to examination, please amend the application as follows:

In the Specification:

On page 1 of the specification, under the title, please amend by inserting the following:

--This application claims priority to PCT application PCT/CA00/00266 filed March 13, 2000, which claims priority to Canadian Application No. 2,265,396, filed March 12, 1999.--

Please create a new page of the specification for the abstract as follows:

-- Compounds of general formula (I), wherein  $R_1$  is H or C1 to C3 alkyl;  $R_2$  is aryl or  $-(CH_2)_n$ -aryl and n is 1 to 4;  $R_3$  is H or  $CH_3$ ; and  $R_4$  is substituted or unsubstituted phenyl, pyridyl, thiophene, furan, indole, pyrrole, thiazole or imidazole are described, as well as methods for treating cell proliferative disorders and neoplastic disorders.--

In the Claims:

Please replace Claims 34-36 as follows:

(Amended) 34. A method in accordance with claim 23 wherein the neoplastic disorder is a lymphoma, a leukemia or a metastatic carcinoma.

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(Amended) 36. A method for treating a cell proliferative disorder in a mammal comprising administering to the mammal an effective amount of a compound in accordance with claim 1.

Enclosed is the following Exhibit A:

Exhibit A: Marked-up Version of Amendments to the Claims.

**Remarks**

The claims have been amended to eliminate multiple claim dependencies. The changes to the claims are editorial and do not constitute new matter. Entry of the amendment is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition



PATENT

Docket No. 280502000200

International Application No. PCT/CA00/00266

for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 280502000200.

However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: September 11, 2001

By: Karen Babrak Dow  
Karen B. Dow  
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## EXHIBIT A

## MARKED-UP VERSION OF AMENDMENTS TO THE CLAIMS

(Amended) 34. A method in accordance with [any one of claims 23 to 33] claim 23 wherein the neoplastic disorder is a lymphoma, a leukemia or a metastatic carcinoma.

(Amended) 35. A method in accordance with [any one of claims 23 to 33] claim 34 wherein the neoplastic disorder is Acute Lymphoblastic Leukemia.

(Amended) 36. A method for treating a cell proliferative disorder in a mammal comprising administering to the mammal an effective amount of a compound in accordance with [any one of claims 1 to 11] claim 1.

## METHODS AND COMPOSITIONS FOR TREATING LEUKEMIA

### Field of the Invention

This invention relates to tyrphostins or benzylidene malononitrile  
5 compounds which are useful as antiproliferative pharmaceuticals for treating  
a variety of cell proliferative disorders.

### Background of the Invention

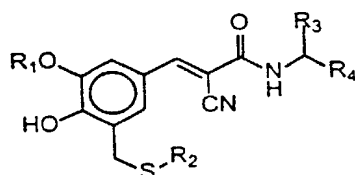
A number of tyrphostins or benzylidene malononitrile derivatives have  
10 been described which are tyrosine kinase inhibitors and are effective to inhibit  
cell proliferation, for example in human leukemia (United States Patents Nos.  
5,217,999 and 5,773,476).

### Summary of the Invention

15 The present invention provides a new group of tyrphostins or  
benzylidene malononitrile derivatives of improved effectiveness as inhibitors  
of cell growth.

In accordance with one embodiment, the compounds of the invention  
have the general formula:

20



25

wherein

R<sub>1</sub> is H or C1 to C3 alkyl;

30

R<sub>2</sub> is aryl or -(CH<sub>2</sub>)<sub>n</sub>- aryl and n is 1 to 4;

$R_3$  is H or  $CH_3$ ; and

$R_4$  is substituted or unsubstituted phenyl, pyridyl, thiophene, furan, indole, pyrrole, thiazole or imidazole.

In accordance with a further embodiment, the compounds have the  
5 general formula I above, wherein

$R_1$  is H, methyl or ethyl;

$R_2$  is phenyl, benzyl,  $-(CH_2)_2$ -phenyl,  $-(CH_2)_3$ -phenyl or 2-thiobenzothiazole;

$R_3$  is H; and

10  $R_4$  is phenyl.

In accordance with a preferred embodiment, the compounds are those shown in Figures 2 to 6.

In accordance with a further embodiment, the invention provides a pharmaceutical composition comprising as active ingredient a compound of  
15 formula I above.

In accordance with a further embodiment, the invention provides a pharmaceutical composition comprising as active ingredient one of the compounds shown in Figures 2 to 6.

In accordance with a further embodiment, the invention provides a  
20 method for treating a cell proliferative disorder in a mammal comprising administering to the mammal an effective amount of a compound of formula I above.

In accordance with a further embodiment, the invention provides a method for treating a cell proliferative disorder in a mammal comprising  
25 administering to the mammal an effective amount of at least one of the compounds shown in Figures 2 to 6.

In accordance with a further embodiment, the invention provides a method for treating a neoplastic disorder in a mammal comprising  
30 administering to the mammal an effective amount of a compound of formula I above.

In accordance with a preferred embodiment, the invention provides a method for treating acute lymphoblastic leukemia (ALL) in a mammal comprising administering to the mammal an effective amount of a compound of formula I above.

5 In accordance with a further preferred embodiment, the invention provides a method for treating acute lymphoblastic leukemia (ALL) in a mammal comprising administering to the mammal an effective amount of at least one of the compounds shown in Figures 2 to 6.

# 10 Summary of the Drawings

Figure 1 shows in schematic form a process for synthesising the compounds of the invention.  $R_1$  is C1 to C3 alkyl;  $R_2$  is aryl or  $-(CH_2)_n$ -aryl, where n is 1 to 4;  $R_3$  is H or  $CH_3$ ; and  $R_4$  is substituted or unsubstituted phenyl, pyridyl, thiophene, furan, indole, pyrrole, thiazole or imidazole.

15 Figures 2 to 6 show some examples of the compounds of the invention.

Figure 7 shows the inhibitory effect (expressed as colony formation/ $1.5 \times 10^5$  cells) of several compounds of the invention on growth of G2 ALL cells.

20 Figure 8 shows the inhibitory effect of several compounds of the invention on growth of G2 ALL cells.

Figures 9, 10, 11 and 12 show the effect of compounds AG 1977, AG 1978, AG 2009 and AG 2010 respectively on the growth of normal BM cells, as indicated by three different assays.

25 Figure 13 shows inhibition of G2 ALL cells by various concentrations of the compounds of the invention.

Figure 14 shows a dose response curve of G2 ALL cell inhibition and AG 2009 concentration.

Figure 15 shows inhibition C1 ALL cells by various concentrations of AG 1977 and 1978.



R<sub>4</sub> is substituted or unsubstituted phenyl, pyridyl, thiophene, furan, indole, pyrrole, thiazole or imidazole.

The compounds of the invention are prepared by the process shown schematically in Figure 1. The required aldehydes (a) are available

5 commercially or can be synthesised as previously described (Gazit et al., (1993), J. Med. Chem., v. 36, p. 3556). Benzyl cyano acetamide (b) is synthesised as described previously (Gazit et al., (1991), J. Med. Chem., v. 34, p. 1896).

10 A preferred group of compounds are the compounds shown in Figures 2 to 6.

The compounds of the invention may be used to treat a variety of neoplastic disorders, including leukemia, lymphomas, metastatic carcinomas and other forms of cancer. Leukemias which may be treated include B-  
15 lineage Acute Lymphoblastic Leukemia (ALL), such as the aggressive Philadelphia\* leukemia, and acute myelocytic leukemia and juvenile myelo monocytic leukemia; lymphomas which may be treated include B-lineage Burkitt's lymphoma and Non-Hodgkin's lymphomas, such as the Ki-1 positive anaplastic large cell lymphomas.

The compounds of the invention may also be used to reduce or inhibit  
20 cell growth in a variety of cell proliferative disorders such as inflammatory disorders, allergic disorders, autoimmune diseases and graft rejection. situations in which cell growth suppression, and preferably T cell growth suppression, is desired.

The compounds of the invention may also be used to inhibit the activity  
25 of Jak2 kinase. They may therefore be used to treat any disorder associated with increased or undesired Jak2 kinase activity.

The compounds of this invention may be used in the form of the free base, in the form of salts and as hydrates. All forms are within the scope of the invention. Acid addition salts may be formed and provide a more  
30 convenient form for use; in practice, use of the salt form inherently amounts to

use of the base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the beneficial properties inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of the basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt per se is desired only as an intermediate product as, for example, when the salt is formed only for the purposes of purification and identification, or when it is used as an intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures.

Pharmaceutically acceptable salts within the scope of the invention include those derived from the following acids; mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like.

Compounds may be examined for their efficacy in inhibiting cell growth in cell proliferation assays such as those described herein.

In accordance with the methods of the invention, the described tyrphostins may be administered to a leukemia patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compositions of the invention may be administered orally or parenterally, the latter route including intravenous and subcutaneous administration. Parenteral administration may be by continuous infusion over a selected period of time.

The active compound may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may







was added and the reaction extracted with ethyl acetate. Evaporation and trituration with dichloromethane-hexane gave 340 mg, 78% yield. yellow solid, mp-195°.

NMR (acetone d<sub>6</sub>) δ 8.08(1H,s,vinyl), 7.62(1H,d,J=2.2 Hz), 7.3(11H,m), 4.58(2H,s), 3.78(2H,s), 3.75(2H,s).

MS m/e-430(M<sup>+</sup>,16%), 175(100%).

**Compound AG 1951: N-benzyl-2-cyano-3-(3'-ethoxy-4'-hydroxy-5'-methylene thiophenyl phenyl) acrylamide**

R<sub>1</sub> = CH<sub>2</sub>CH<sub>3</sub>, R<sub>2</sub> = phenyl, R<sub>3</sub> = H, R<sub>4</sub> = phenyl

(c) 500 mg 1.74mM 3-ethoxy-4-hydroxy-5-methylene thiophenyl benzaldehyde, 310 mg 1.78 mM N-benzyl cyano acetamide and 25 mg β-alanine in 40 mL ethanol were refluxed 4 hours. Evaporation and trituration with hexane gave 730 mg yellow solid, 95% yield, mp-108°.

NMR (acetone d<sub>6</sub>) δ 8.10(1H,s,vinyl), 7.70(1H,d,J=2.2 Hz), 7.53(1H,d,J=2.2 Hz), 7.3(10H,m), 4.58(2H,d,J=6.0 Hz), 4.26(2H,s), 4.18(2H,q,J=7.0 Hz), 1.42(3H,t,J=7.0 Hz).

**Compound AG 1978: N-benzyl-2-cyano-3-(3',4-dihydroxy-5'-methylene thiophenyl phenyl) acrylamide**

R<sub>1</sub> = H, R<sub>2</sub> = phenyl, R<sub>3</sub> = H, R<sub>4</sub> = phenyl

(d) To 200 mg of product from (c) in 30 mL dichloromethane was added 0.4 mL BBr<sub>3</sub>. After stirring 1 hour at room temperature water was added and the reaction extracted with ethyl acetate. Evaporation and trituration with dichloromethane-hexane gave 91 mg, 47% yield. yellow solid, mp-175°.

NMR (acetone d<sub>6</sub>) δ 8.01(1H,s,vinyl), 7.63(1H,d,J=2.2 Hz), 7.3(11H,m), 4.58(2H,s), 4.26(2H,s).

MS m/e- 416(M<sup>+</sup>,16%), 309(12), 263(32), 196(37), 175(100%).



NMR (CDCl<sub>3</sub>)  $\delta$  8.25(1H,s,vinyl), 7.62(1H,d,J=2.2 Hz), 7.3(11H,m),  
4.61(2H,d,J=6.0 Hz), 3.96(3H,s), 3.81(2H,s), 2.69(2H,t,J=6.0 Hz),  
2.50(2H,t,J=6.0 Hz), 1.90(2H,quint.,J=6.0 Hz).

5 **Compound AG 2010: N-benzyl-2-cyano-3-(3',4'-dihydroxy-5'-  
(methylene thiopropyl phenyl) phenyl) acrylamide**

R<sub>1</sub> = H, R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Ph, R<sub>3</sub> = H, R<sub>4</sub> = phenyl

(h) To 660 mg of product from (g) in 25 mL dichloromethane was  
added 0.6 mL BBr<sub>3</sub>. After stirring 1 hour at room temperature water  
10 was added and the reaction extracted with ethyl acetate. Evaporation  
and trituration with dichloromethane-hexane gave 610 mg, 95% yield.  
yellow solid, mp-138°.

NMR (acetone d<sub>6</sub>)  $\delta$  8.17(1H,s,vinyl), 7.63(1H,d,J=2.2 Hz), 7.3(11H,m),  
4.58(2H,s), 3.80(2H,s), 2.69(2H,t,J=6.0 Hz), 2.52(2H,t,J=6.0 Hz),  
15 1.90(2H,quint.,J=6.0 Hz).

**Compound AG 1976: N-benzyl-2-cyano-3-(3',4'-dihydroxy-5'-  
methylene (2'-thiobenzothiazole) phenyl) acrylamide**

R<sub>1</sub> = H, R<sub>2</sub> = 2-thiobenzothiazole, R<sub>3</sub> = H, R<sub>4</sub> = phenyl

20 (i) 330 mg, 1 mM, 4-hydroxy-3-methoxy-5-methylene (2-thio-  
benzothiazole) benzaldehyde, 180 mg, 1.03 mM, N-benzyl cyano  
acetamide and 15 mg  $\beta$ -alanine in 20 ml ethanol were refluxed 4  
hours. Cooling and filtering gave 460 mg, 95% yield, yellow solid.

25 (j) To 200 mg, 0.4 mM, solid from (i) in 30 ml dichloromethane was  
added 0.4 ml BBr<sub>3</sub>. After stirring 1 hour at room temperature, water  
and 3 ml HCl was added and the reaction extracted with ethyl acetate.  
Evaporation and trituration with dichloromethane-hexane gave 40 mg,  
20% yield, bright yellow solid, mp-225°.



methycellulose supplemented with 30% FCS (Cansera Rexdale, Ont.) or normal human plasma, a cocktail of cytokines consisting of G-CSF (10 ng/ml, Amgen), IL-3 (40 U/ml, Immunex), MGF (50 ng/ml, Immunex), Erythropoietin (2u/ml, Epprex) or TPO (10 ng/ml, Amgen) and  $5 \times 10^{-5}$  2-mercaptoethanol.

5 The culture mixture was plated in 1 ml volumes into 35 mm petri dishes and incubated at 37°C with 5% CO<sub>2</sub> in a humidified atmosphere with concentrations of tyrphostin up to 40 µM. The results are shown in Figures 9 to 12.

The BFU-E's (erythroid colonies) and the CFU-GEMM (mixed colonies) 10 exhibited inhibition at and above 25µM (Fig. not shown), while the CFU-C's (granulocytes, monocytes and macrophages) showed a dramatic increase of colony proliferation peaking at 25µM and a reduction by 50µM (Fig. not shown). AG 2010 showed significant inhibition at 40µM, while the remaining compounds showed mild to significant inhibition of erythroid and mixed 15 colonies followed by the myeloid population at 20µM.

#### **Example 4 - Inhibition of ALL Cells**

Various concentrations of tyrphostins were tested for inhibition of ALL cells in the clonogenic assay described in Example 2. Compounds AG 1977, 20 1978, 2007, 2008, 2009 and 2010 were tested against ALL cell lines A1, C1 and G2 in doses ranging from nanomolar to micromolar values. The results are shown in Figures 8, 13, 15 and 16.

AG 2009 demonstrated the most potent clonogenic inhibition, in a dose responsive manner, against G2 cells (Fig. 13). It showed a greater than 50% 25 inhibition at a dose of 16nM and a differential therapeutic index of greater than 2 logs in a survival curve (Fig. 14) of normal BM and G2 colonies.

#### **Example 5 - Inhibition of Blast Cells**

The compounds were further tested in an ALL blast colony assay, against bone marrow samples from two patients with pre -B ALL phenotype based on their FAB classification.

The ALL blast colony assay was performed as described previously (Estrov, Z. et al., (1988), Cancer Res., v. 48, p. 5901) with some modifications. Briefly, heparinized bone marrow cells were layered over Percoll (density 1.077 g/l; Pharmacia Fine Chemicals Piscataway, N.J.) and centrifuged (400g) for 10 minutes at 4°C to remove neutrophils and RBC's. The collected interphase fraction was further enriched for lymphoblasts before plating by using a magnetic cell separator, mini MACS, with separation column (Miltenyi Biotec Inc., 1250 Oakmead Park, Sunnyvale, Ca). With this procedure, ALL blasts were specifically isolated from the marrow mononuclear cell fraction using directly labelled MACS CD19 Microbeads - monoclonal anti-human CD19 (Mouse IgG1, Kappa- Miltenyi Biotec Inc.) and/or indirect magnetic cell labeling using primary biotinylated antibody- (mouse anti-human CD10 monoclonal antibody, Caltag Laboratires, Ca.) and Streptavidin Microbeads (Miltenyi Biotech Inc.). The resulting cell population was composed of 99% lymphoblasts. The positively sorted cells were then cultured at  $2 \times 10^5$  cells/ml in alpha MEM (GIBCO) containing 0.9% (vol/vol) methylcellulose supplemented with 10% FCS (Cansera, Rexdale, Ont.). Irradiated autologous leukemic blasts were used as feeder cells (at  $3 \times 10^5$  cells/ml). Cytokines, normally used, were deleted so that only spontaneous proliferation was evident.

The culture mixture was plated into 35mm petri dishes (Nunc, GIBCO) containing 1ml volumes and incubated at 37°C with 5% CO<sub>2</sub> in a humidified atmosphere. Colonies containing more than 20 cells were scored, using inverted microscope, at 5-7 days.

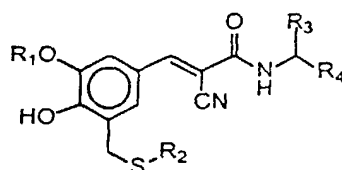
In both cases, significant inhibition of blast colonies was observed (See for example, Figure 17).





WE CLAIM:

1. A compound of the general formula:



wherein

$R_1$  is H or C1 to C3 alkyl;

$R_2$  is aryl or  $-(CH_2)_n$ - aryl and n is 1 to 4;

$R_3$  is H or  $CH_3$ ; and

$R_4$  is substituted or unsubstituted phenyl, pyridyl, thiophene, furan, indole, pyrrole, thiazole or imidazole.

2. A compound in accordance with claim 1 wherein

$R_1$  is H, methyl or ethyl;

$R_2$  is phenyl, benzyl,  $-(CH_2)_2$ -phenyl,  $-(CH_2)_3$ -phenyl or 2-thiobenzothiazole;

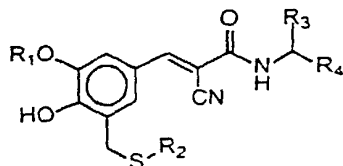
$R_3$  is H; and

$R_4$  is phenyl.

3. A compound in accordance with claim 1 wherein the compound is N-benzyl-2-cyano-3-(4'-hydroxy-3'-methoxy-5'-methylene thiobenzyl phenyl) acrylamide.



12. A pharmaceutical composition comprising a compound of the formula:



10 wherein

$R_1$  is H or C1 to C3 alkyl;

$R_2$  is aryl or  $-(CH_2)_n-$  aryl and n is 1 to 4;

$R_3$  is H or  $CH_3$ ; and

15  $R_4$  is substituted or unsubstituted phenyl, pyridyl, thiophene, furan, indole, pyrrole, thiazole or imidazole and a pharmaceutically acceptable carrier.

13. A pharmaceutical composition in accordance with claim 12 comprising a compound of formula I, wherein

20  $R_1$  is H, methyl or ethyl;

$R_2$  is phenyl, benzyl,  $-(CH_2)_2$ -phenyl,  $-(CH_2)_3$ -phenyl or 2-thiobenzothiazole;

$R_3$  is H; and

$R_4$  is phenyl.

25

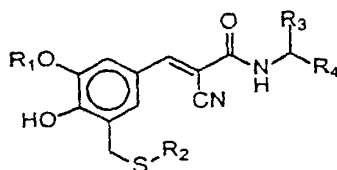
14. A pharmaceutical composition in accordance with claim 12 wherein the compound is N-benzyl-2-cyano-3-(4'-hydroxy-3'-methoxy-5'-methylene thiobenzyl phenyl) acrylamide.



22. A pharmaceutical composition in accordance with claim 12 wherein the compound is N-benzyl-2-cyano-3-(3',4'-dihydroxy-5'-(methylene thiopropyl phenyl) phenyl) acrylamide.

5 23. A method for treating a neoplastic disorder in a mammal comprising administering to the mammal an effective amount of a compound of the formula:

10



I

15

wherein

R<sub>1</sub> is H or C1 to C3 alkyl;

R<sub>2</sub> is aryl or -(CH<sub>2</sub>)<sub>n</sub>- aryl and n is 1 to 4;

20

R<sub>3</sub> is H or CH<sub>3</sub>; and

R<sub>4</sub> is substituted or unsubstituted phenyl, pyridyl, thiophene, furan, indole, pyrrole, thiazole or imidazole.

24. A method in accordance with claim 23 comprising administering an effective amount of a compound of formula I wherein

25

R<sub>1</sub> is H, methyl or ethyl;

R<sub>2</sub> is phenyl, benzyl, -(CH<sub>2</sub>)<sub>2</sub>-phenyl, -(CH<sub>2</sub>)<sub>3</sub>-phenyl or 2-thiobenzothiazole;

R<sub>3</sub> is H; and

30

R<sub>4</sub> is phenyl.

25. A method in accordance with claim 23 wherein the compound is N-benzyl-2-cyano-3-(4'-hydroxy-3'-methoxy-5'-methylene thiobenzyl phenyl) acrylamide.
- 5
26. A method in accordance with claim 23 wherein the compound is N-benzyl-2-cyano-3-(3'-ethoxy-4'-hydroxy-5'-methylene thiophenyl phenyl) acrylamide.
- 10
27. A method in accordance with claim 23 wherein the compound is N-benzyl-2-cyano-3-(3',4'-dihydroxy-5'-methylene (2'-thiobenzothiazole) phenyl) acrylamide.
- 15
28. A method in accordance with claim 23 wherein the compound is N-benzyl-2-cyano-3-(3',4'-dihydroxy-5'-methylene thiobenzyl phenyl) acrylamide.
29. A method in accordance with claim 23 wherein the compound is N-benzyl-2-cyano-3-(3',4'-dihydroxy-5'-methylene thiophenyl phenyl) acrylamide.
- 20
30. A method in accordance with claim 23 wherein the compound is N-benzyl-2-cyano-3-(4'-hydroxy-3'-methoxy-5'-(methylene thioethyl phenyl) phenyl) acrylamide.
- 25
31. A method in accordance with claim 23 wherein the compound is N-benzyl-2-cyano-3-(4'-hydroxy-3'-methoxy-5'-(methylene thiopropyl phenyl) phenyl) acrylamide.
- 30
32. A method in accordance with claim 23 wherein the compound is N-benzyl-2-cyano-3-(3',4'-dihydroxy-5'-(methylene thioethyl phenyl) phenyl) acrylamide.

33. A method in accordance with claim 23 wherein the compound is N-benzyl-2-cyano-3-(3',4'-dihydroxy-5'-(methylene thiopropyl phenyl) phenyl) acrylamide.

5

34. A method in accordance with any one of claims 23 to 33 wherein the neoplastic disorder is a lymphoma, a leukemia or a metastatic carcinoma.

35. A method in accordance with any one of claims 23 to 33 wherein the  
10 neoplastic disorder is Acute Lymphoblastic Leukemia.

36. A method for treating a cell proliferative disorder in a mammal comprising administering to the mammal an effective amount of a compound in accordance with any one of claims 1 to 11.

15

37. A method in accordance with claim 36 wherein the cell proliferative disorder is selected from the group consisting of an inflammatory disorder, an allergic disorder, an autoimmune disease or graft rejection.



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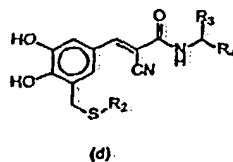
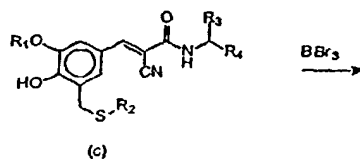
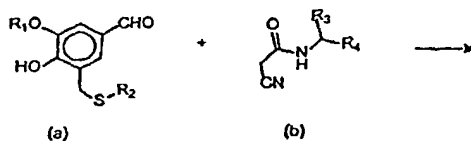
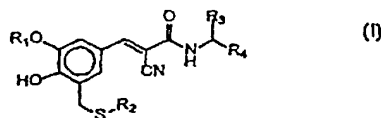
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : C07C 323/60, C07D 277/74, A61K 31/277, 31/428, A61P 35/02		A1	(11) International Publication Number: WO 00/55128
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(71) Applicants (for all designated States except US): HSC RESEARCH AND DEVELOPMENT LIMITED PARTNERSHIP [CA/CA]; Suite 5270, 555 University Avenue, Toronto, Ontario M5G 1X8 (CA). YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM [IL/IL]; Jabotinsky Street 46, P.O. Box 4279, 91042 Jerusalem (IL).		Published With international search report.	
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(54) Title: METHODS AND COMPOSITIONS FOR TREATING LEUKEMIA

## (57) Abstract

Compounds of general formula (I), wherein R<sub>1</sub> is H or C1 to C3 alkyl; R<sub>2</sub> is aryl or -(CH<sub>2</sub>)<sub>n</sub>-aryl and n is 1 to 4; R<sub>3</sub> is H or CH<sub>3</sub>; and R<sub>4</sub> is substituted or unsubstituted phenyl, pyridyl, thiophene, furan, indole, pyrrole, thiazole or imidazole are described, as well as methods for treating cell proliferative disorders and neoplastic disorders.



1/17

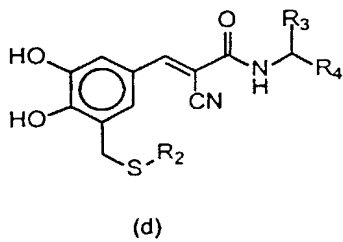
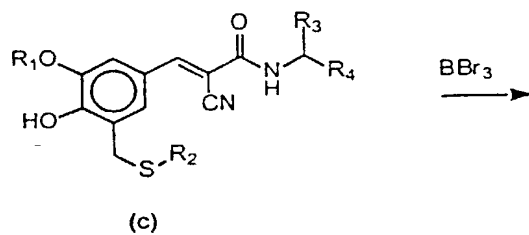
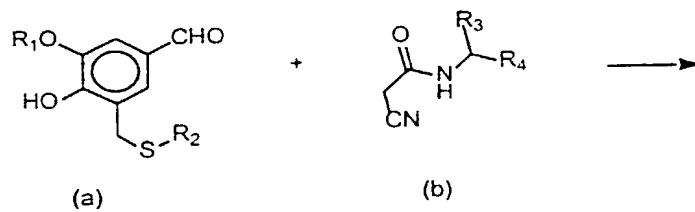


Figure 1

2/17

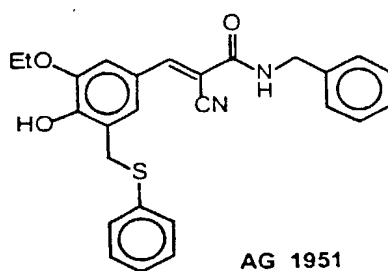
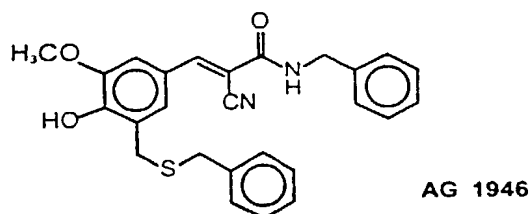
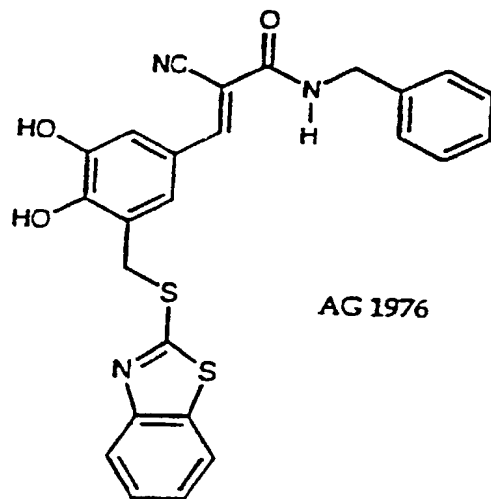
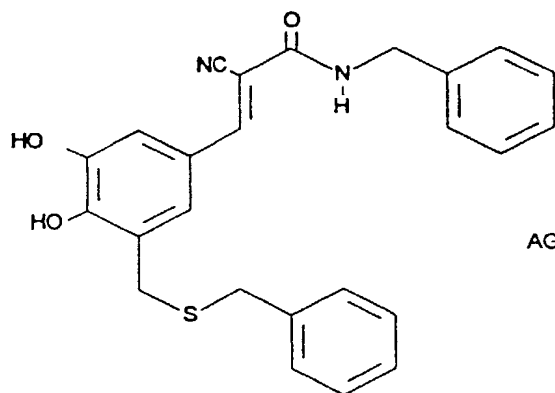


Figure 2

3/17



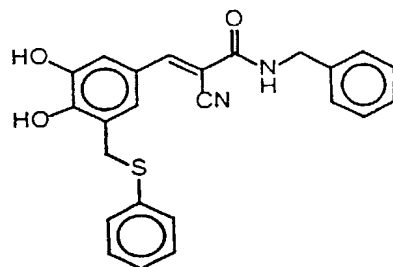
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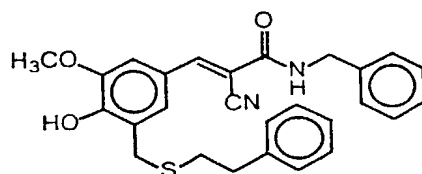
AG 1977

Figure 3

4/17



AG 1978



AG 2007

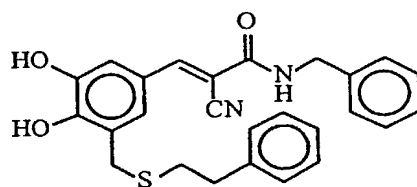
Figure 4

COc1cc(C=C(C#N)C(=O)NCC2=CC=CC=C2)ccc(SCCC3=CC=CC=C3)c1O

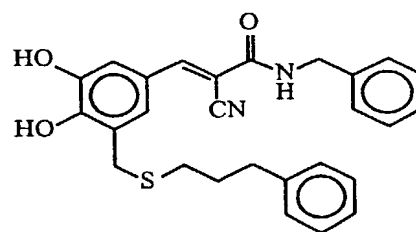
AG 2008

Figure 5

6/17



AG 2009



AG 2010

Figure 6

WO 00/55128

PCT/CA00/00266

7/17

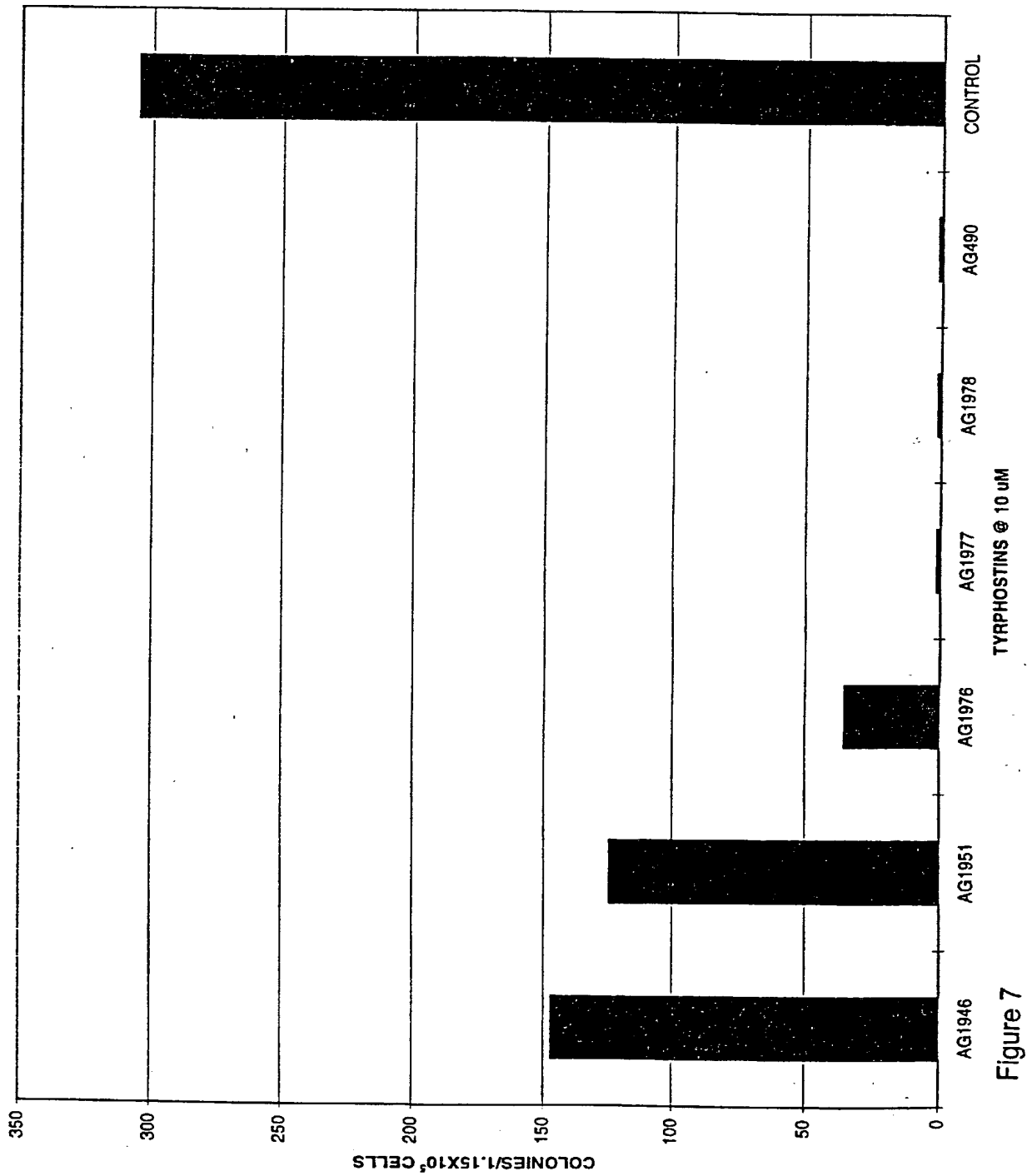


Figure 7



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PCT/CA00/00266

8/17

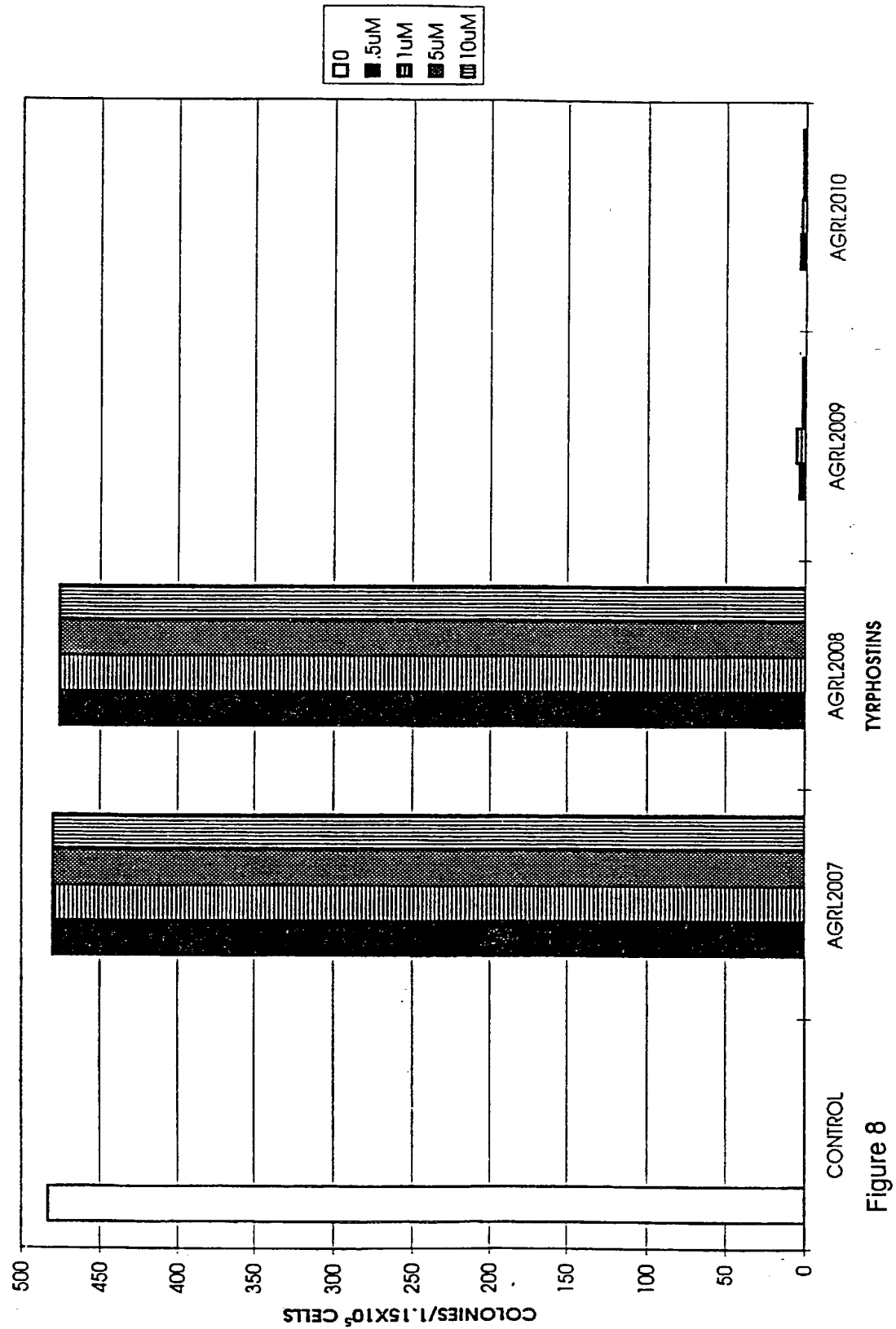


Figure 8

9/17

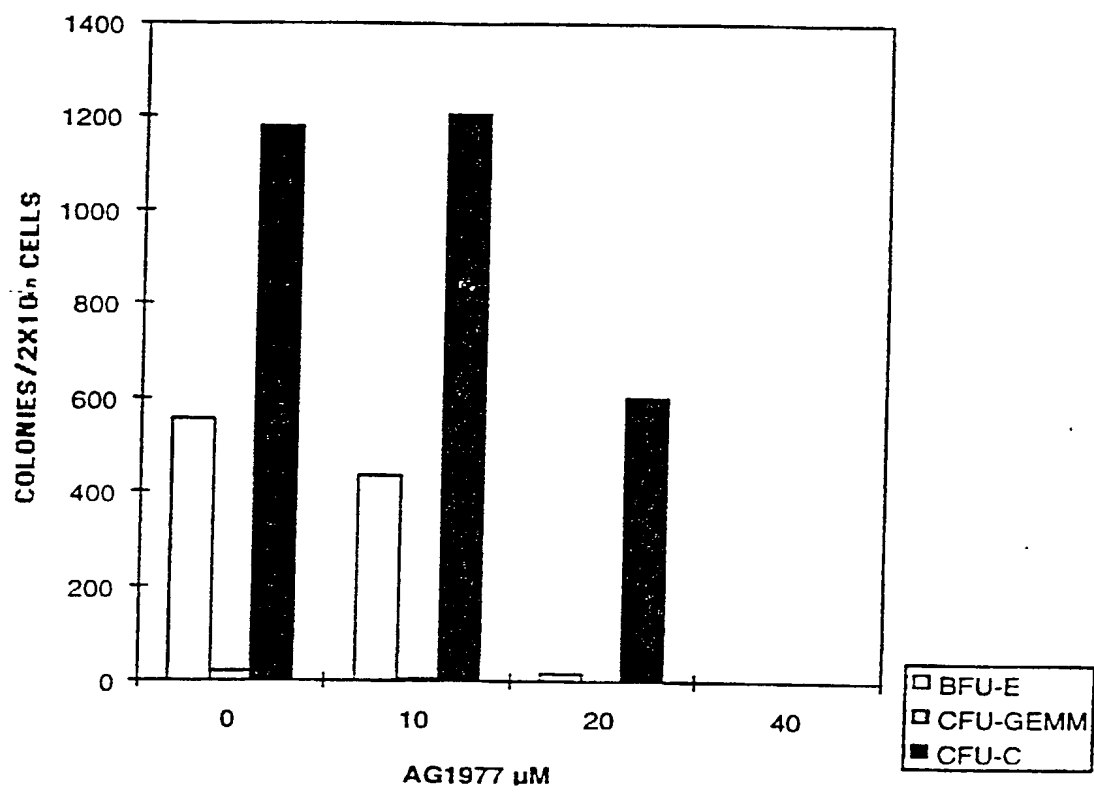


Figure 9

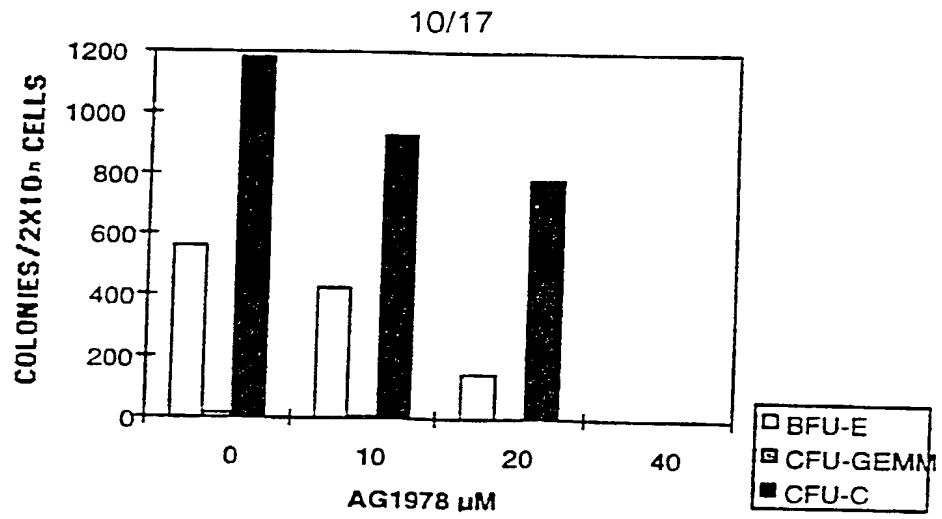


Figure 10

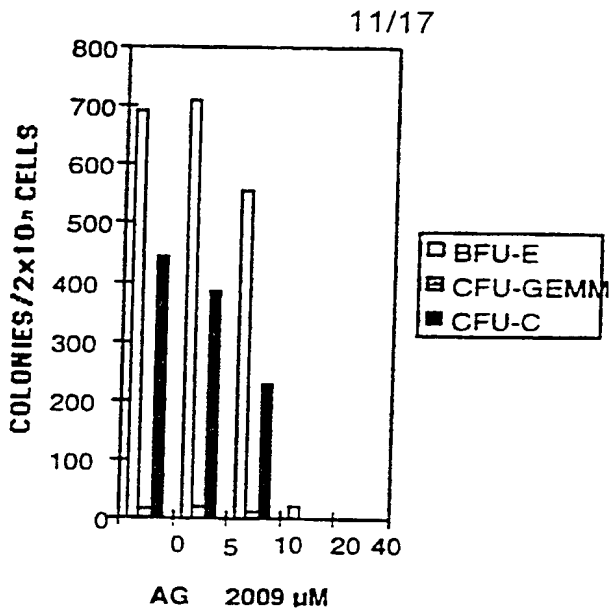


Figure 11

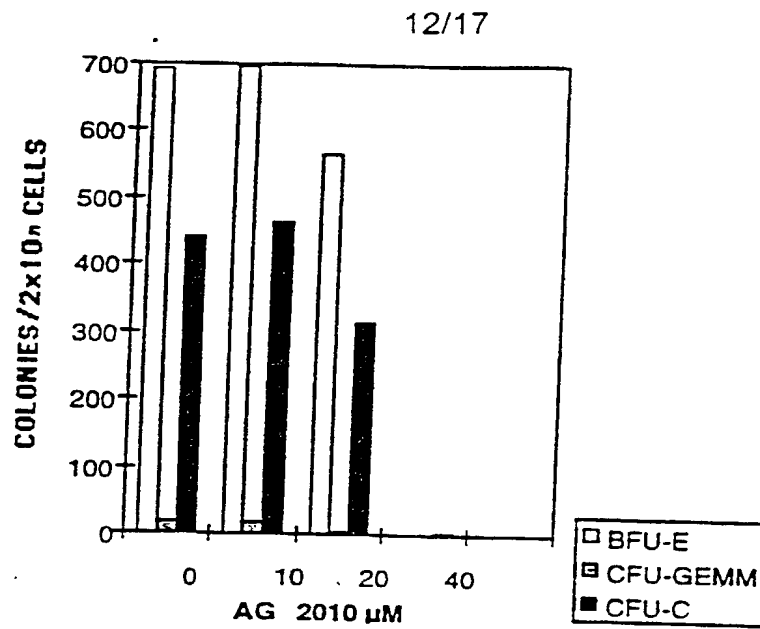


Figure 12

13/17

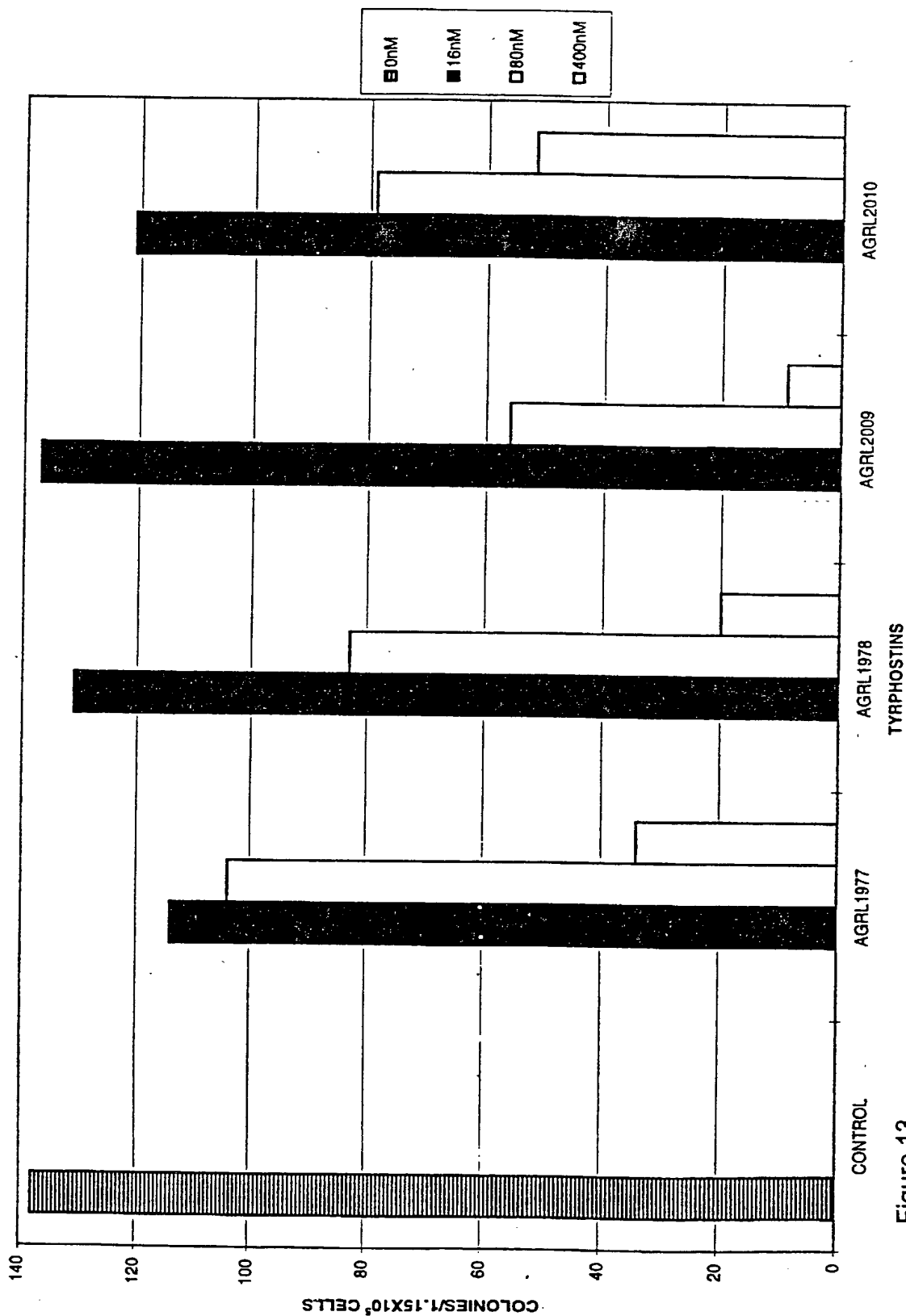


Figure 13

14/17

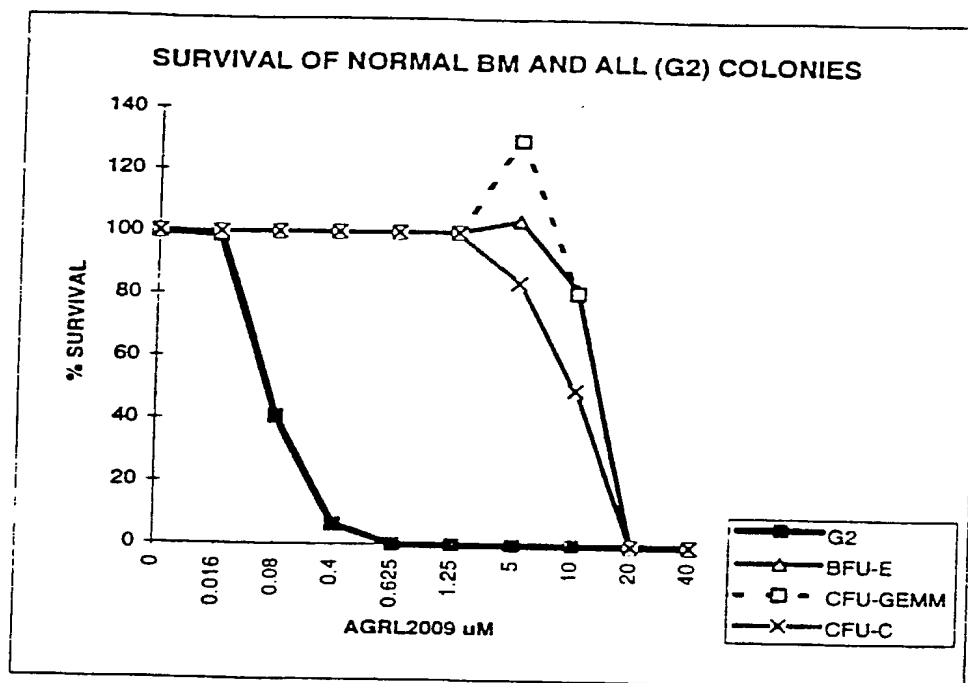


Figure 14

15/17

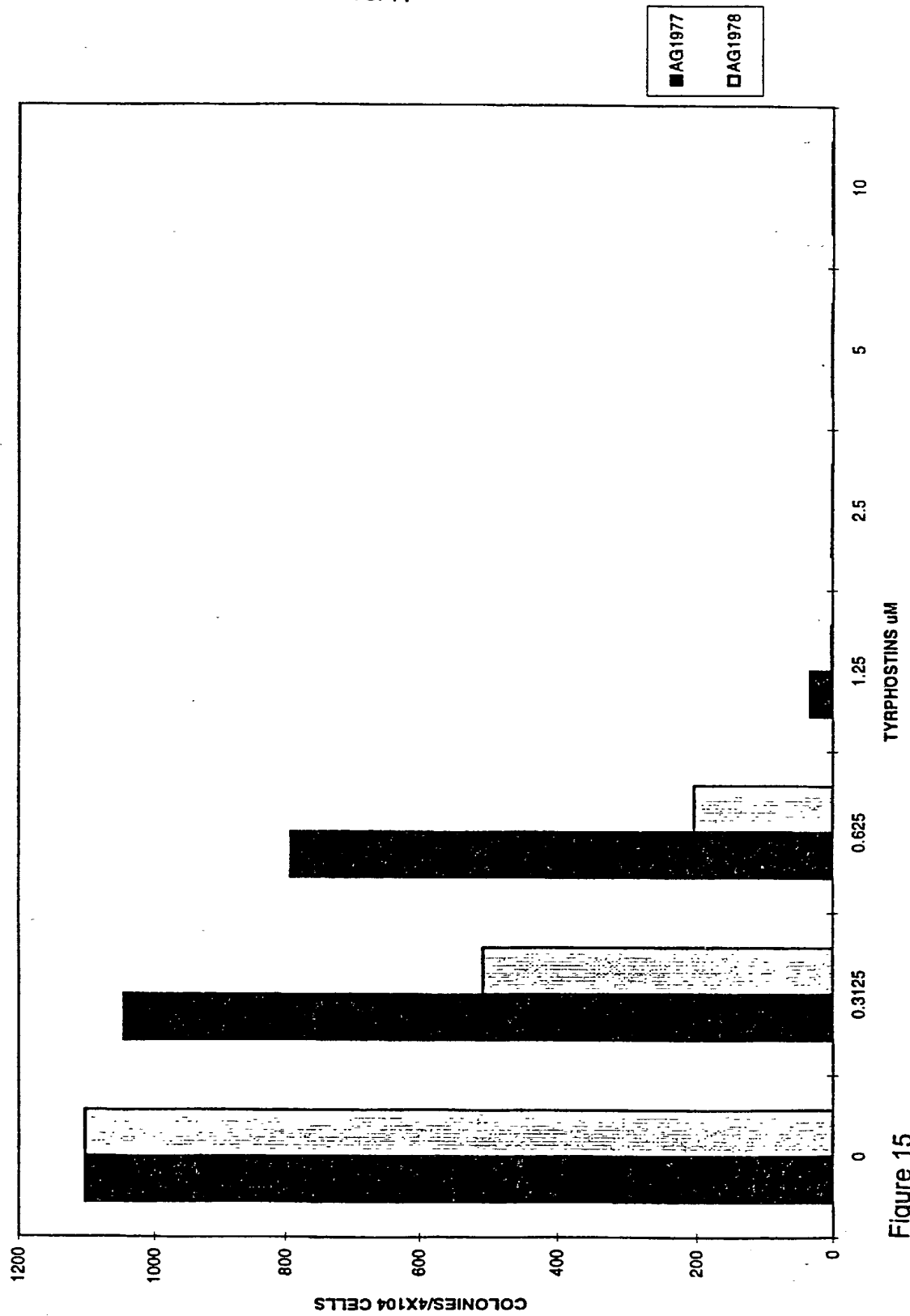


Figure 15



EO  
 0.4uM  
 2uM

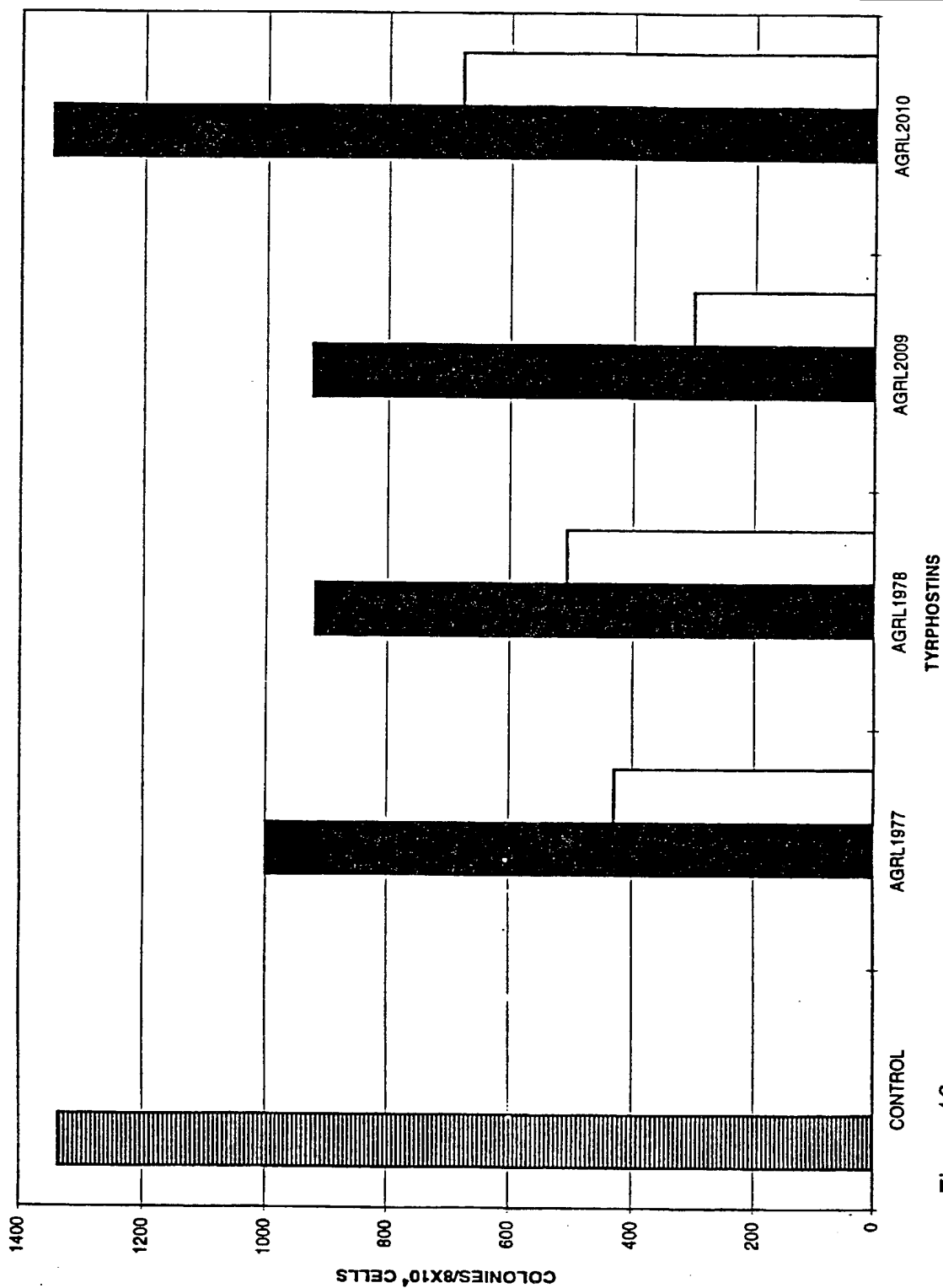


Figure 16

17/17

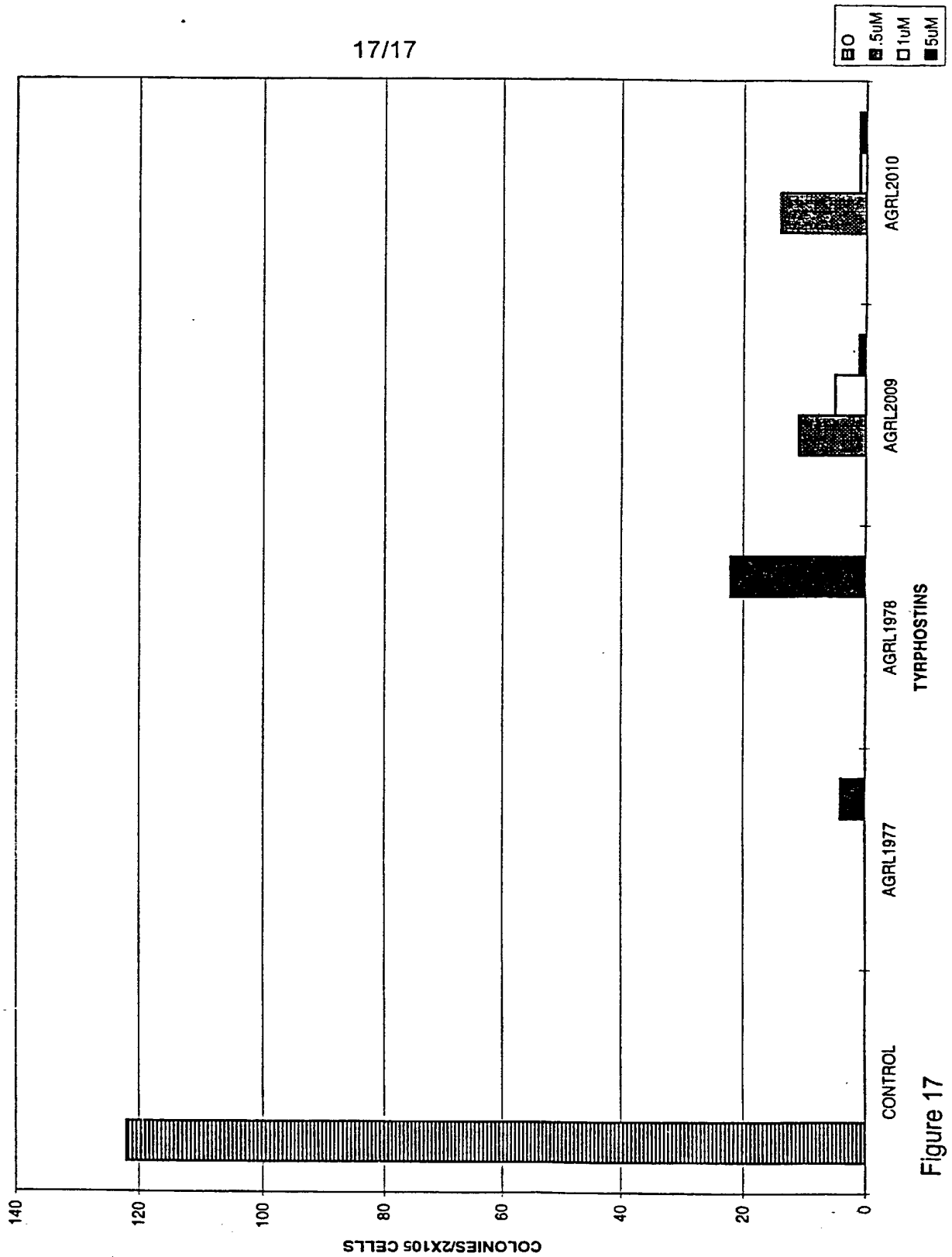


Figure 17

PATENT  
Docket No. 28050200020

# DECLARATION FOR UTILITY PATENT APPLICATION

AS A BELOW-NAMED INVENTOR, I HEREBY DECLARE THAT:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: METHODS AND COMPOSITIONS FOR TREATING LEUKEMIA, the specification of which is attached hereto unless the following box is checked:

- ☒ was filed on September 11, 2001 as United States Application Serial No. 09/936,887 and on March 13, 2000 as PCT International Application No. PCT/CA00/00266.

I HEREBY STATE THAT I HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE.

I acknowledge the duty to disclose information which is material to the patentability as defined in 37 C.F.R. § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed:

Application No.	Country	Date of Filing (day/month/year)	Priority Claimed?
PCT/CA00/00266	PCT	13 March 2000	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
2,265,396	CA	12 March 1999	

I hereby claim benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Application Serial No.	Filing Date
*	

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to

patentability as defined in 37 C.F.R. § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status
*		<input type="checkbox"/> Patented <input type="checkbox"/> Pending <input type="checkbox"/> Abandoned

I hereby appoint the following attorneys and agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

75-

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Madeline I. Johnston (Reg No. <u>36,174</u> )	Parisa Jorjani (Reg No. <u>46,813</u> )
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Gladys H. Monroy (Reg No. <u>32,430</u> )	Philip A. Morin (Reg No. <u>P-45,926</u> )
Kate H. Murashige (Reg No. <u>29,959</u> )	Paul S. Naik (Reg No. <u>P49,075</u> )
Mabel Ng (Reg No. <u>P48,922</u> )	Martin M. Noonan (Reg No. <u>44,264</u> )
Catherine M. Polizzi (Reg No. <u>40,130</u> )	Phillip Reilly (Reg No. <u>41,415</u> )
Debra A. Shetka (Reg No. <u>33,309</u> )	Terri Shieh-Newton (Reg No. <u>47,081</u> )
Rebecca Shortle (Reg No. <u>47,083</u> )	Kevin R. Spivak (Reg No. <u>43,148</u> )
Stanley H. Thompson (Reg No. <u>45,160</u> )	Thomas L. Treffert (Reg No. <u>P48,279</u> )
Brenda J. Wallach (Reg No. <u>45,193</u> )	Michael R. Ward (Reg No. <u>38,651</u> )
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patentability as defined in 37 C.F.R. § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status
*		<input type="checkbox"/> Patented <input type="checkbox"/> Pending <input type="checkbox"/> Abandoned

I hereby appoint the following attorneys and agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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PATENT  
Docket No. 28050200020

### DECLARATION FOR UTILITY PATENT APPLICATION

AS A BELOW-NAMED INVENTOR, I HEREBY DECLARE THAT:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: METHODS AND COMPOSITIONS FOR TREATING LEUKEMIA, the specification of which is attached hereto unless the following box is checked:

- ☒ was filed on September 11, 2001 as United States Application Serial No. 09/936,887 and on March 13, 2000 as PCT International Application No. PCT/CA00/00266.

I HEREBY STATE THAT I HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE.

I acknowledge the duty to disclose information which is material to the patentability as defined in 37 C.F.R. § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed:

Application No.	Country	Date of Filing (day/month/year)	Priority Claimed?
PCT/CA00/00266	PCT	13 March 2000	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
2,265,396	CA	12 March 1999	

I hereby claim benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Application Serial No.	Filing Date
*	

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to

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 Peter J. Yim (Reg No. 44,417)  
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David T. Yang (Reg No. 44,415)  
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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